Impairment of Coronary Microvascular Dilation in Response to Cold Pressor–Induced Sympathetic Stimulation in Type 2 Diabetic Patients With Abnormal Stress Thallium Imaging

Alain Nitenberg, Séverine Ledoux, Paul Valensi, Régis Sachs, Jean-Raymond Attali, and Isabelle Antony

Coronary microcirculation dysfunction may be associated with myocardial perfusion defects on thallium imaging in diabetic patients without coronary artery stenosis. Microvascular coronary adaptation to increased myocardial oxygen demand in response to sympathetic stimulation evoked by the cold pressor test was examined in 22 type 2 diabetic patients with thallium imaging defects and in 15 control subjects. Both the diabetic patients and control subjects had angiographically normal coronary arteries and no other risk factors. Despite a similar increase in the rate-pressure product in the two groups (22.6 ± 12.4% in diabetic patients and 31.8 ± 8.2% in control subjects, NS), coronary blood flow increase in the left anterior descending artery (mean flow velocity measured by intracoronary Doppler multiplied by the cross-sectional area measured by digital angiography) was significantly lower in diabetic patients than in control subjects (14.7 ± 19.8 vs. 75.5 ± 13.5%, respectively; P = 0.0001). In addition, when there was a positive correlation between the two parameters in control subjects (r = 0.651, P < 0.01), there was no relationship in diabetic patients (r = 0.054). In conclusion, vasodilation of the coronary microcirculation in response to sympathetic stimulation evoked by the cold pressor test is impaired in type 2 diabetic patients without epicardial artery lesions. This microvascular impairment during sympathetic stimulation may explain exercise-induced myocardial perfusion abnormalities observed in these patients and may impair microcirculatory coronary vasodilation during current life stress episodes such as exercise, mental stress, or cold exposition. *Diabetes* 50:1180–1185, 2001

It has been shown that endothelium-dependent epicardial coronary artery vasodilation in response to acetylcholine (1) or physiological stimuli (2) is impaired in diabetic patients with angiographically normal coronary arteries. Microvascular functional abnormalities have also been reported by Nasher et al. (3), who have shown that metabolic vasodilation of coronary microcirculation evoked by atrial pacing is reduced in diabetic patients. Similar impairment has also been reported in hypertensive patients with angiographically normal coronary arteries (4) and by Zeiher et al., who showed that coronary blood flow failed to increase during exercise (5) or during the cold pressor test (CPT) in patients with early atherosclerosis (6) and without significant coronary artery stenosis, suggesting that the endothelial function is impaired at the microvascular level. Such coronary microcirculation dysfunction may be associated with myocardial perfusion defects on 99mTc sestamibi single photon emission computed tomography (SPECT) imaging in humans with angina and minimally obstructive coronary artery disease (7) and might contribute to myocardial ischemia when myocardial oxygen demand is increased, even in the absence of coronary artery stenosis.

In diabetes, it has been suggested that coronary functional abnormalities and microvascular structural alterations (8–12) might contribute to the development of left ventricular dysfunction through episodes of silent myocardial ischemia when myocardial oxygen demand is increased (13) and might explain the high frequency of exercise thallium imaging defects. However, in diabetic patients, there are no data on coronary microvascular vasomotion in response to sympathetic stimulation, which is a current situation during normal human activity.

Therefore, the present study was designed to evaluate the coronary microvascular adaptation to increased myocardial oxygen demand in response to sympathetic stimulation evoked by the CPT in type 2 diabetic patients with abnormal SPECT stress thallium scintigraphy, angiographically normal coronary arteries, and no other coronary risk factors.

**RESEARCH DESIGN AND METHODS**

**Patient selection.** A total of 22 patients with type 2 diabetes undergoing diagnostic coronary angiography were included in this study. These patients were selected from 92 diabetic patients referred for coronary arteriography...
because of abnormal SPECT stress thallium scintigraphy. All patients had a normal electrocardiogram or nonspecific T-wave abnormalities. Mean duration of diabetes was 12.5 ± 8.1 years, and all patients manifested proper glucose homeostasis at the time of catheterization, as shown by fasting and postprandial plasma glucose (≤5.5 ± 1.3 and ≤6.4 ± 1.5 mmol/l, respectively) and HbA1c (5.1 ± 1.4%). The control group was composed of 15 patients with a normal electrocardiogram who were referred for coronary arteriography because of symptoms suggestive of angina, and/or an equivocal exercise treadmill test, and with normal stress thallium scintigraphy.

Patients with a history of arterial hypertension (blood pressure >140/90 mmHg), patients (untreated or treated with lipid-lowering therapy) with a total cholesterol level >5.0 mmol/l or LDL cholesterol >3.70 mmol/l (143 mg/dl), smokers, patients >65 years of age, and postmenopausal women without substitutive hormonal therapy were excluded. None of the patients had a family history of premature coronary artery disease (defined as a first-degree relative aged <60 years with clinical evidence of coronary atherosclerosis). All patients had normal left ventricular systolic function and mass assessed by two-dimensional and M-mode echocardiography (14,15) and abnormal SPECT stress thallium scintigraphy.

Patients were included in the present study by consensus of two experienced investigators upon immediate review of the angiograms and only if coronary arteries were angiographically normal and completely smooth, without luminal irregularities. The study protocol was approved by the Institutional Review Committee of the University of Kremlin-Bicêtre. All patients gave written informed consent before cardiac catheterization.

**Catheterization protocol.** Patients were studied in the fasting state. No premedication was administered; 1% lidocaine was used for local anesthesia, and 5,000 U intravenous heparin was administered. After documentation of normal coronary arteries, an additional 5,000 U i.v. heparin was given, and an 8F guiding catheter was positioned in the left coronary artery. Each patient then underwent the following study protocol. A 3F 20-MHz coronary Doppler catheter (Monorail Doppler 3; Schneider Europe, Zurich, Switzerland) connected to a single-channel 20-MHz pulsed Doppler velocimeter (model MDV-20 Single Channel V; Millar Instruments, Houston, TX) was placed in the left anterior descending artery (LAD). The catheter position was adjusted to obtain an optimal audio signal and phasic tracing of coronary blood flow velocity. The use of this device to assess intracoronary blood flow velocity has been previously discussed in detail (16).

**Protocol design.** Thirty minutes after the coronary arteriography, the first hemodynamic measurements and left coronary arteriography (baseline) were carried out. Five minutes later, the CPT was performed. The patients’ hands were immersed in ice water for 120 s. Coronary angiograms were performed using an injection of 8 ml low-osmolality contrast medium (meglumine diatrizoate) in the left coronary artery, at baseline, and at the peak of the CPT (immediately before removal of the hands from ice water). Serial injections of the left coronary artery were performed at intervals of at least 5 min to exclude coronary stenosis-induced coronary dilation. At the end of the protocol, coronary flow reserve was measured by injecting 12 mg papaverine into the left coronary artery (17) 4 min after intracoronary infusion of a bolus of 2 mg isosorbide dinitrate.

**Quantitative coronary arteriography.** Left coronary arteriograms were obtained by electrocardiogram-triggered digital subtraction at a rate of six frames per second on a 512-pixel matrix (General Electric CGR DG 300; General Electric, Issy-les-Moulineaux, France). The angiographic system was set up in a right anterior oblique position with adequate cranial or caudal angulation, allowing an optimal view of the LAD segment on end-diastolic frames without overlap by side branches. Relationships among focal spot, patient, and height of image tube were kept constant throughout the procedure. Analysis of coronary angiograms and measurement of coronary artery diameter were performed by a previously validated technique (16). The accuracy of the technique was 3.6 ± 0.5% (mean ± SD), and the precision was 2.4 ± 0.9%. The maximum error between the actual and the calculated diameter was equal to ±5.7% ($v^2 = 0.994$). In this study, a segment of the guiding catheter filled with saline was placed close to the center of the image and used for calibration for the procedure before the procedure was begun.

**Measurements.** Intracoronary blood flow velocity was measured in the LAD at the tip of the Doppler catheter just before each angiogram to avoid the hemodynamic artifact of the contrast material. Heart rate, aortic pressure (through the guiding catheter), mean and phasic blood flow velocity (kilohertz shift), and electrocardiogram were continuously monitored throughout the protocol. Measurements of the diameter of the LAD were made on each angiogram. Cross-sectional area (CSA) of the LAD was calculated from the diameter (d) assuming a circumferential model: $CSA = πd^2/4$. Each angiogram was analyzed at random without knowledge of the sequence of the procedure (baseline, CPT, or after isosorbide dinitrate). Estimates of blood flow ($F$) in the LAD were calculated from measurements of mean coronary flow velocity in the LAD ($v$) and LAD-CSA ($F = v \times CSA$). Coronary flow reserve was calculated as the peak-to-resting coronary flow velocity ratio (18).

**Statistical analysis.** All data are expressed as means ± SD. Differences between the two groups of patients for clinical and biological characteristics and basal hemodynamic parameters were compared by the nonparametric Mann-Whitney U test. The paired Student’s t test was used for intragroup statistical comparisons of hemodynamic parameters and LAD blood flow under baseline and CPT. Comparisons between diabetic patient and control subject data were made using the unpaired Student’s t test. Comparison of LAD dimensions at baseline, during CPT, and after intracoronary isosorbide dinitrate was made by two-way analysis of variance with repeated measures for experimental condition factor, followed by the Fisher’s protected least significant differences test. Statistical significance was assumed if the null hypothesis could be rejected at the 0.05 probability level.

### RESULTS

**Characteristics of the two study groups.** Characteristics of the two groups of patients are summarized in Table 1. The two groups were not different with regard to sex ratio, age, lipid profile, and heart rate. Although the two groups had arterial pressure within normal values, systolic pressure was mildly but significantly higher in diabetic patients than in control subjects. Diastolic pressure was comparable in the two groups.

**Hemodynamic changes due to CPT.** Heart rate was similar at baseline, but increased significantly during CPT only in control subjects. Systolic pressure was slightly higher at baseline in diabetic patients and increased significantly in the two groups during CPT, the level of systolic pressure being comparable in the two groups during CPT. Mean arterial pressure was comparable at baseline and during the CPT in the two groups, with a significant increase in both groups (22.6 ± 12.4% in diabetic patients and 31.8 ± 8.2% in control subjects; $P = 0.0001$ vs. baseline for the two groups) (Table 2).

**Coronary blood flow changes.** CSA of the LAD was...
similar at baseline in the two groups, but during the CPT, coronary arteries constricted in diabetic patients and dilated in control subjects (Table 2). This abnormal response in diabetic patients has been previously reported and is due to an abnormal endothelium-dependent vasodilation (1,2). Conversely, endothelium-independent coronary artery dilation (isosorbide dinitrate) was preserved in diabetic patients (1,2) and was similar to that of control subjects (44 ± 17 vs. 38 ± 15%, respectively; NS).

Flow velocity in the left anterior descending coronary artery was higher at baseline in diabetic patients and was similar in the two groups during CPT (Table 2). At baseline, although coronary blood flow was higher in the diabetic patients, the difference between the two groups was not significant (Fig. 1). During CPT, coronary blood flow was comparable in the two groups. However, increase in coronary blood flow in diabetic patients was mild when compared with the dramatic increase observed in control subjects (14.7 ± 19.8 vs. 75.5 ± 13.5%, respectively; P = 0.0001) (Fig. 1). Lastly, when there was a significant correlation between coronary blood flow increase and rate-pressure product rise in control subjects, there was no correlation between these two variables in diabetic patients (Fig. 2).

Coronary flow reserve measured at the end of the protocol was lower in diabetic patients than in control subjects (Table 2). This depression of coronary flow reserve in diabetic patients has been previously reported (1,3). Nevertheless, the ability of coronary blood flow to increase remained important in the diabetic group.

**DISCUSSION**

The major finding of the present study was that type 2 diabetic patients with angiographically normal coronary arteries and no other coronary risk factors and who have abnormal SPECT stress thallium scintigraphy, showed a mismatch between change in coronary blood flow and increase in myocardial oxygen demand during sympathetic stimulation by the CPT, whereas papaverine was able to substantially vasodilate the coronary microcirculation. Such an impairment of metabolic microvascular coronary vasodilation as been shown in diabetic rat hearts (19) and in diabetic patients in response to atrial pacing by Nasher et al. (3). However, in the latter study, other coronary risk factors that could impair microvascu-

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Diabetic patients (n = 22)</th>
<th>Control subjects (n = 15)</th>
<th>P (diabetic patients vs. control subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart rate (bpm)</td>
<td>73 ± 9</td>
<td>74 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>134 ± 11</td>
<td>161 ± 11†</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>97 ± 8</td>
<td>116 ± 11†</td>
<td>NS</td>
</tr>
<tr>
<td>Rate-pressure product (mmHg × heart rate)</td>
<td>9,714 ± 1,262</td>
<td>11,852 ± 1,513†</td>
<td>NS</td>
</tr>
<tr>
<td>LAD-CSA (mm²)</td>
<td>5.82 ± 2.15</td>
<td>5.02 ± 1.78†</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Flow velocity (cm/s)</td>
<td>10.2 ± 2.3</td>
<td>13.3 ± 2.7†</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>3.91 ± 0.92</td>
<td>4.88 ± 0.52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are means ± SD. *P < 0.01, †P < 0.001 vs. baseline.

### FIG. 1

Coronary blood flow in LAD in the two groups of patients at baseline (□) and during the CPT (■).

### FIG. 2

Relationship between changes in left anterior descending coronary blood flow and in the rate-pressure product induced by the CPT in the two groups of patients. There was a significant correlation between the two parameters in only the control subjects.
lar metabolic vasodilation were not taken into account. In our study, because other confounding factors that have been demonstrated to impair metabolic dilation of coronary microcirculation such as hypercholesterolemia (20), hypertension (21), cigarette smoking (22), and coronary atherosclerosis (23–26) were excluded, results clearly show that diabetes is an independent factor of coronary microvascular dysfunction.

**CPT and coronary vasomotion.** Cold pressor stimulation induces sympathetic release of norepinephrine and epinephrine (25), which evokes an increase in heart rate, arterial blood pressure (26), and myocardial oxygen demand. In dogs and in healthy subjects, this increase in myocardial metabolic demand has been shown to cause an increase in coronary blood flow and to dilate epicardial coronary arteries (26,27), despite the α-adrenergic–mediated coronary stimulation of smooth muscle cells. This dilation of the coronary vascular bed is modulated by the endothelium through an α₂-receptor–mediated release of nitric oxide (NO), which facilitates vasodilatation of resistance vessels (28), and flow-dependent dilation in large vessels (29). The overall effect is an increase in coronary blood flow matched to the myocardial oxygen demand. Because rate-pressure product increase (Table 2), which roughly represents the increase in myocardial oxygen demand, was similar in diabetic patients and in control subjects, we reasonably should have observed a similar increase in coronary blood flow in the two groups of patients. In our study, because the age of diabetic patients and control subjects was not significantly different, age could not contribute to blunted coronary blood flow during the CPT (23,24).

**Mechanisms leading to impaired metabolic vasodilation in coronary microcirculation of diabetic patients.** Because structural changes of coronary microcirculation (medial hypertrophy, fibromuscular hyperplasia, intimal proliferation, and perivascular fibrosis) have been shown in diabetic patients (8–12) and may be responsible for the reduction of maximal coronary blood flow and coronary reserve (1,3), the uncoupling between coronary microvascular adaptation and myocardial oxygen demand during sympathetic stimulation by the CPT might be explained by the inability of microvessels to dilate. Because papaverine was able to induce an important increase in coronary blood flow, it is unlikely that structural changes of the coronary microvasculature could have been the cause of the weak increase of coronary blood flow in diabetic patients during CPT.

It has been well established that diabetes and hyperglycemia impair peripheral and epicardial coronary artery endothelial function (1,2,19,30–37). The responses of epicardial coronary arteries to the CPT were abnormal in our diabetic patients, evidence of a decrease in coronary CSA, suggesting an impairment of endothelium-dependent dilation. This result is comparable to our previous data in these patients (1,2). However, constriction was moderate (−12.7 ± 12.4% CSA decrease), and it is unlikely that only the constriction of a nonstenosed coronary artery during the CPT could have impeded coronary blood flow increase.

In the absence of stenosis in large epicardial coronary arteries, coronary blood flow adaptation to myocardial oxygen demand depends mainly on the microcirculatory vasomotion (38). Several factors might be implicated in the impairment of physiological metabolic vasodilation of coronary microcirculation in diabetes. Thus, endothelial dysfunction at the microvascular level has been shown in diabetic rats (19) and in diabetic patients in response to atrial pacing (3).

Although the level of glycemia was not measured before the evaluation of coronary microvascular vasodilation, it is unlikely that our results could be due to hyperglycemia because it seems highly improbable that our patients, who were studied in the fasting state in the morning, were hyperglycemic at the time of the investigation. An increased production of vasoconstrictor prostaglandins has been shown in diabetic rabbit aorta (39). However, Williams et al. (30) have shown that vasoconstrictor prostanoids do not contribute to forearm microvascular dysfunction in diabetic patients. Thromboxane A₂ biosynthesis, a vasoconstrictive product of activated platelets, is also enhanced in diabetic patients (40).

The impairment might also be due to an abnormal production or destruction of NO, to abnormal membrane NO receptor–messenger interactions, or to reduced sensitivity of smooth muscle cells to NO. Although our study does not allow us to differentiate between these different mechanisms, in contrast to Williams et al., in forearm vessels, we did not find any decreased reactivity vascular smooth muscle cells of epicardial coronary arteries to nitrates (1,2). Moreover, the abnormal response cannot be explained by a reduced availability of NO due to a deficit of L-arginine, the natural precursor of NO, as suggested by Giugliano et al. (32), because we failed to show any improvement of epicardial coronary artery dilation after L-arginine infusion in diabetic patients (2).

On the other hand, we previously demonstrated that an intracoronary low dose of deferoxamine, an iron chelator that prevents iron-catalyzed generation of hydroxyl radicals, could restore a normal vasodilation of epicardial coronary arteries in response to CPT in diabetic patients, suggesting that NO could be inactivated by oxygen-derived free radicals (2). Indeed, it is well known that superoxide anions inactivate NO directly (41), and that in diabetic patients, cellular oxidant stress is enhanced (42) in vessel walls by advanced glycation end products (AGEs) (43) resulting from nonenzymatic glycation and oxidation. AGEs have been linked to the development of vasculopathy (44,45), mainly through binding to specific AGE receptors (RAGES) that are expressed by endothelial cells (46), and interaction between AGEs and RAGEs induces cellular oxidant stress (43) that can inactivate NO. Free radicals can also generate vasoconstrictor and platelet activator 8-iso-prostaglandin F₂α (47,48), which is increased in diabetes. This agent, which has been demonstrated to be produced by porcine vascular smooth muscle cells in hyperglycemic conditions, can be reduced by antioxidant supplementation by vitamin E in diabetic patients (49). Moreover, plasma from diabetic patients has been demonstrated to have less antioxidant capacity than plasma in normal subjects (50), and it has been shown that antioxidant vitamin C can restore forearm endothelium-dependent vasodilation of the microcirculation in type 2 diabetic patients (31).

Lastly, the impairment of metabolic coronary microvas-
cular dilation could also result from an imbalance between α-adrenergic constriction, β-adrenergic dilation (down-regulation), and endothelium-derived vasodilation mediated by NO. Indeed, in experimental diabetes, an increased sensitivity to α-adrenergic stimulation has been shown (51,52). On the other hand, β-adrenergic vasodilation might be impaired at the coronary microvascular level because of downregulation of β-adrenergic receptors that are predominant in the coronary microcirculation. However, Nasher et al. (3) showed that β-adrenergic antagonist therapy does not influence the reduction of coronary resistance during atrial pacing. Whatever the NO system dysfunction, NO and nitrates are not the only dilators acting on coronary microvasculature, and an abnormality lying at the NO level might not be the sole culprit of the abnormal coronary microvascular vasodilation. Then, further studies are needed to address the underlying mechanisms that could explain the nonadaptation of coronary blood flow to myocardial metabolic demand in diabetic patients.

**Methodological considerations.** All of our patients had angiographically normal coronary arteries, and it can be questioned why, for example, a patient with a deficit in the inferior area on thallium imaging may have an abnormal response to CPT in the left anterior descending coronary artery. It must be pointed out that a thallium defect depends on a contrast between two areas that have different myocardial blood flow, and not only between an area of normal perfusion and an underperfused area. Thus, because the vascular response to sympathetic stimulation is heterogeneous, it is possible that in diabetic patients, myocardial blood flow could be reduced differently in adjacent regions, resulting in a heterogeneous myocardial perfusion that could cause thallium defects.

The use of a crystal end-mounted catheter with a zero-crossing detector Doppler velocimeter might not have provided accurate measurements of coronary flow velocity (53). However, this limitation has been raised for measurements of flow velocity in stenosed coronary arteries. In addition, it has been demonstrated that velocities recorded simultaneously by the former method and by spectral Doppler guide wire technique are not significantly different (54). Thus, the major results of our study should be valid.

Although the diabetic patients we studied had no angiographically normal coronary arteries, and it can be questioned why, for example, a patient with a deficit in the inferior area on thallium imaging may have an abnormal response to CPT in the left anterior descending coronary artery. It must be pointed out that a thallium defect depends on a contrast between two areas that have different myocardial blood flow, and not only between an area of normal perfusion and an underperfused area. Thus, because the vascular response to sympathetic stimulation is heterogeneous, it is possible that in diabetic patients, myocardial blood flow could be reduced differently in adjacent regions, resulting in a heterogeneous myocardial perfusion that could cause thallium defects.

Coronary flow reserve was evaluated by the maximal-to-basal coronary flow ratio estimated through the peak-to-resting flow velocity ratio. This technique has been extensively validated, but it does not measure absolute flows and does not allow the determination of whether the reduction in coronary reserve is due to an elevated resting flow or to a reduced maximal flow. In this study, basal coronary blood flow in diabetic patients was slightly but not significantly higher than that in control subjects, which could partly explain the lower coronary flow reserve in diabetic patients.

**Clinical implications.** In diabetic patients, coronary endothelial dysfunction is impaired in large epicardial coronary arteries and in the microcirculation. This endothelial dysfunction leads to a mismatch between myocardial oxygen demand increase and supply that could explain thallium scintigraphic myocardial perfusion defects suggestive of myocardial ischemia in these patients (7). Because exercise is a potent sympathetic stimulus, and because diabetic patients are often asymptomatic, episodes of myocardial ischemia might be frequent in diabetic patients, even when epicardial coronary arteries do not show significant stenosis, as has been previously reported in patients with impaired endothelium-dependent coronary vasodilation of other etiologies (2). Then, silent myocardial perfusion impairment could participate in progressive left ventricular dysfunction that leads to the dilated cardiomyopathy described in diabetic patients without significant coronary artery stenosis (26,27).

Hence, in diabetic patients, treatment of coronary endothelial dysfunction should target coronary microcirculation as well as epicardial coronary arteries. Because oxidative stress is increased in diabetes, drugs that have antioxidant effects—vitamins C and E or ACE inhibitors—might be of interest to prevent episodes of silent ischemia that could lead to progressive deterioration of the myocardium and potentiate the specific detrimental effects of diabetes on myocardium, even in patients without significant coronary artery stenosis. However, although there is considerable evidence for increased oxidative stress in diabetes, the impact of oxidative stress on endothelial-mediated vasomotion abnormalities in diabetes needs further investigation.

**Conclusion.** Functional and anatomical abnormalities of the coronary microcirculation distinct from epicardial coronary atherosclerosis might be responsible for myocardial ischemia and/or hypoxia, which may contribute to oxidative stress that leads to the remodeling of the diabetic heart and development of cardiomyopathy in the absence of coronary atherosclerosis. Thus, the increased sympathetic activity that is observed in diabetes (52) may impair microcirculatory coronary vasodilation during current life stress episodes (exercise, mental stress, or cold exposition) and explain myocardial perfusion defects on exercise thallium SPECT imaging.

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